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Jon W Dudas

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

SUBSTITUTED THIOPHENES AND USES THEREOF

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 46
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☐ Drawing(s) *Number of Sheets* _____
☐ Other (specify) _____
☐ Application Data Sheet. See 37 CFR 1.76

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☐ Applicant claims small entity status. See 37 CFR 1.27.
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Respectfully submitted,

SIGNATURE Karen Kondrad

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Docket Number: 101064-3 US

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SUBSTITUTED THIOPHENES AND USES THEREOF

Field of the invention

The present invention relates to novel substituted thiophenes, their pharmaceutical compositions and methods of use. In addition, the present invention relates to therapeutic methods for the treatment and prevention of cancers.

Background of the invention

Chemotherapy and radiation exposure are currently the major options for the treatment of cancer, but the utility of both these approaches is severely limited by adverse effects on normal tissue, and the frequent development of tumor cell resistance. It is therefore highly desirable to improve the efficacy of such treatments in a way that does not increase the toxicity associated with them. One way to achieve this is by the use of specific sensitizing agents such as those described herein.

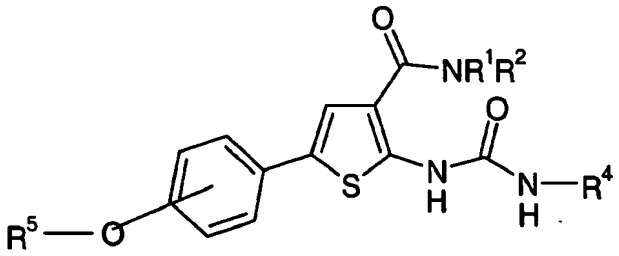
An individual cell replicates by making an exact copy of its chromosomes, and then segregating these into separate cells. This cycle of DNA replication, chromosome separation and division is regulated by mechanisms within the cell that maintain the order of the steps and ensure that each step is precisely carried out. Invovled in these processes are the cell cycle checkpoints (Hartwell *et al.*, *Science*, Nov 3, 1989, 246(4930):629-34) where cells may arrest to ensure DNA repair mechanisms have time to operate prior to continuing through the cycle into mitosis. There are two such checkpoints in the cell cycle – the G1/S checkpoint that is regulated by p53 and the G2/M checkpoint that is monitored by the Ser/Thr kinase checkpoint kinase 1 (CHK1).

The cell cycle arrest induced by these checkpoints is a mechanism by which cells can overcome the damage resulting from radio- or chemotherapy, their abrogation by novel agents should increase the sensitivity of tumor cells to DNA damaging therapies. Additionally, the tumor specific abrogation of the G1/S checkpoint by p53 mutations in the majority of tumors can be exploited to provide tumor selective agents. One approach to the design of chemosensitizers

that abrogate the G2/M checkpoint is to develop inhibitors of the key G2/M regulatory kinase CHK1, and this approach has been shown to work in a number of proof of concept studies. (Koniaras *et al.*, *Oncogene,* 2001, 20:7453; Luo *et al.*, *Neoplasia*, 2001, 3:411; Busby *et al.*,*Cancer Res.*, 2000, 60:2108; Jackson *et al.*, *Cancer Res.*, 2000, 60:566).

Summary of the invention

Provided herein are novel compounds of structural formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 are at each occurrence independently selected from H, optionally substituted C_{1-6}alkyl, or optionally substituted heterocycle; or R^1 and R^2 and the N to which they are attached in combination form an optionally substituted heterocycle;

R^4 is selected from H, optionally substituted carbocycle, optionally substituted heterocycle, or optionally substituted C_{1-6}alkyl;

R^5 is selected from optionally substituted carbocycle, or optionally substituted C_{1-6}alkyl.

The invention also encompasses stereoisomers, enantiomers, *in vivo*-hydrolysable precursors and pharmaceutically-acceptable salts of compounds of formula I, pharmaceutical compositions and formulations containing them, methods of using them to treat diseases and conditions either alone or in combination with other therapeutically-active compounds or substances, processes and intermediates used to prepare them, uses of them as medicaments, uses

of them in the manufacture of medicaments and uses of them for diagnostic and analytic purposes.

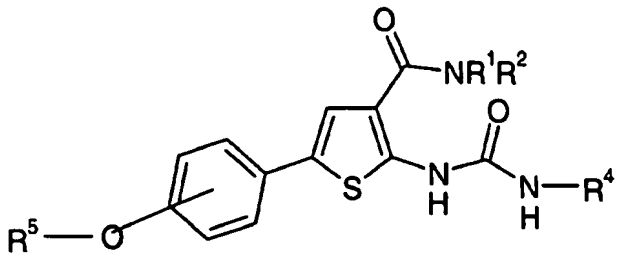
In accordance with the present invention, the applicants have hereby discovered novel compounds that are potent inhibitors of the kinase CHK1 and therefore possess the ability to prevent cell cycle arrest at the G2/M checkpoint in response to DNA damage. These compounds are accordingly useful for their anti-cell-proliferation (such as anti-cancer) activity and are therefore useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said fused compounds, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use with the production of anti-cell proliferation effect in warm-blooded animals such as man.

The present invention includes pharmaceutically acceptable salts or prodrugs of such compounds. Also in accordance with the present invention applicants provide pharmaceutical compositions and a method to use such compounds in the treatment of cancer.

Such properties are expected to be of value in the treatment of disease states associated with cell cycle and cell proliferation such as cancers (solid tumors and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Detailed Description of the Invention

Provided herein are novel compounds of structural formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 are at each occurrence independently selected from H, optionally substituted C_{1-6}alkyl, or optionally substituted heterocycle; or R^1 and R^2 and the N to which they are attached in combination form an optionally substituted heterocycle with the proviso that R^1 and R^2 are not both H;

R^4 is selected from H, optionally substituted carbocycle, optionally substituted heterocycle, or optionally substituted C_{1-6}alkyl;

R^5 is selected from optionally substituted carbocycle, or optionally substituted C_{1-6}alkyl.

In an additional embodiement the present invention provides compounds selected from:

2-({[(4-methoxyphenyl)amino]carbonyl}amino)-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]thiophene-3-carboxamide;

5-{4-[2-(dimethylamino)ethoxy]phenyl}-2-({[(4-methoxyphenyl)amino]carbonyl}amino)thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-2-({[(4-methoxyphenyl)amino]carbonyl}amino)thiophene-3-carboxamide;

2-({[(4-methoxyphenyl)amino]carbonyl}amino)-5-[4-(2-piperidin-1-ylethoxy)phenyl]thiophene-3-carboxamide;

5-{4-[2-(dimethylamino)ethoxy]phenyl}-2-{[(pyridin-3-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-(4-methoxyphenyl)-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

tert-butyl 3-{[(5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}thien-3-yl)carbonyl]amino}piperidine-1-carboxylate;

5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

N-azepan-3-yl-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

N-[3-[(3-aminopyrrolidin-1-yl)carbonyl]-5-(4-methoxyphenyl)thien-2-yl]-N'-pyrazin-2-ylurea;

N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)thien-2-yl]-N'-pyrazin-2-ylurea;

N-(2-aminoethyl)-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

Tert-butyl-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)thien-3-yl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-3-ylthiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1-methylpiperidin-4-yl)thiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-[4-methoxyphenyl)thiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-5-(3,4-dihydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxaminde;

Tert-butyl-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}thien-3-yl)carbonyl]amino)piperidine-1-carboxylate;

Tert-butyl-3-{[(2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}thien-3-yl)carbonyl]amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]thiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-5-(4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-ylthiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl} N-piperidin-3-ylthiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-phenylthiophene-3- carboxaminde;

2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-(3,4-dimethoxyphenyl)thiophene-3- carboxaminde;

2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-bromothiophene-3- carboxaminde;

Tert-butyl-3(S)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}thien-3-yl)carbonyl]amino}piperdine-1-carboxylate

2-[(aminocarbonyl)amino]-5-(4-[2-(diethylamino)ethoxy]phenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-5-(4-[2-(diethylamino)ethoxy]phenyl)-N-[(3R)-piperidin-3-yl]thiophene-3-carboxaminde;

N-2-[(aminoethyl)-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxaminde;

5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid (S)-piperidin-3-ylamide;

5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid (S)-azepan-3-ylamide;

5-(4-Methoxy-phenyl)-2-(3-pyrazin-2-yl-ureido)-thiophene-3-carboxylic acid (S)-azepan-3-ylamide;

tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-[(2*S*)-pyrrolidin-2-ylmethyl]thiophene-3-carboxamide;;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-pyrrolidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-(2-piperidin-1-ylethyl)thiophene-3-carboxamide;

tert-butyl (3*S*)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)pyrrolidine-1-carboxylate;

tert-butyl (3*R*)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-(1,2,3,4-tetrahydroquinolin-3-yl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*S*)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide*tert*-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)azetidine-1-carboxylate;

2-[(aminocarbonyl)amino]-*N*-azetidin-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-*N*-pyrrolidin-3-ylthiophene-3-carboxamide;

tert-butyl 3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-[(3*R*)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-*N*-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*S*)-azepan-3-yl]-5-(3,4-dimethoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-1-azabicyclo[2.2.2]oct-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide;

N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]urea;

2-[(aminocarbonyl)amino]-*N*-(1-ethylpiperidin-3-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

tert-butyl (3*S*)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

tert-butyl (3*R*)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-*N*-[(3*S*)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-*N*-[(3*R*)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*S*)-azepan-3-yl]-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*S*)-1-ethylazepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-(2-aminoethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[2-(dimethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*R*)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-[(3*S*)-1-methylpiperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-[(3*S*)-1-methylazepan-3-yl]thiophene-3-carboxamide;

N-[3-{[(3*S*)-3-aminoazepan-1-yl]carbonyl}-5-(4-methoxyphenyl)-2-thienyl]urea.

In an additional embodiment the present invention provides compounds according to formula I, for use as a medicament.

In an additional embodiment the present invention provides compounds according to formula I, for use, in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with cancer.

In an additional embodiment the present invention provides a method for the treatment of infections associated with cancer comprising administering to a host in need of such treatment a therapeutically effective amount of a compound as set forth in formula I.

In an additional embodiment the present invention provides a method for the prophylaxis treatment of infections associated with cancer comprising administering to a host in need of such treatment a therapeutically effective amount of a compound as set forth in formula I.

In an additional embodiment the present invention provides a method for the treatment or prophylaxis of cancer comprising administering a therapeutically effective amount of a compound as set forth in formula I or a pharmaceutically acceptable salt.

In an additional embodiment the present invention provides a method for the treatment of breast cancer, colorectal cancer, ovarian cancer, lung (non small cell) cancer, malignant brain tumors, sarcomas, melanoma and lymphoma by administring a compound of formula I.

In an additional embodiment the present invention provides a method for the treatment of cancer by administering to a human a compound of claim 1 to 2 and a DNA damaging agent.

In an additional embodiment the present invention provides a pharmaceutical composition comprising a compound as set forth in formula I together with at least one pharmaceutically acceptable carrier, diluent or excipent.

Definitions

The definitions set forth in this section are intended to clarify terms used throughout this application. The term "herein" means the entire application.

As used in this application, the term "optionally substituted," as used herein, means that substitution is optional and therefore it is possible for the designated atom to be unsubstituted. In the event a substitution is desired then such substitution means that any number of hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the normal valency of the designated atom is not exceeded, and that the substitution results in a stable compound. For example when a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. If no selection is provided then the substituent shall be selected from: halogen, nitro, amino, cyano , trifluoromethyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, hydroxy, alkylhydroxy, carbonyl, -$CH(OH)CH_3$, -CH_2NH-alkyl-OH, alkyl-$(OH)CH_3$, -Oalkyl, -OCOalkyl, -NHCHO, -N-(alkyl)-CHO, -NH-CO-amino, -N-(alkyl)-CO-amino, -NH-COalkyl, -N-(alkyl)-COalkyl, -carboxy, -amidino, -CO-amino, -CO-alkyl, -CO_2alkyl, mercapto, -Salkyl, -SO(alkyl), -SO_2(alkyl), -SO_2-amino, -alkylsulfonylamino, phenyl, cycloalkyl, heterocyclic and heteroaryl, -alkly-NH-cycloalkyl, -alkyl-NH-optionally substituted heterocycle, -alkyl-NH-alkyl-OH, -$C(=O)OC(CH_3)_3$, -$N(CH_3)_2$, -alkyl-NH-alkyl-optionally substituted heterocycle, alkyl-aryl, alkyl-polycyclyl, alkyl-amino, alkyl-hydroxy, -CH_2NH-alkyl-heterocycle, -$CH_2NHCH2CH(CH_3)_2$.

If the selection is attached to a ring the substituents could also be selected from: vicinal -O(alkyl)O-, vicinal -O(Chaloalkyl)O-, vicinal -CH_2O(alkyl)O-, vicinal -S(alkyl)S- and –O(alkyl)S-.

When any variable (e.g., R^1, R^4, R^a, R^e etc.) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R^1, then said group may optionally be substituted with 0,1, 2 or 3 R^1 groups and R^e at each occurrence is selected independently from the definition of R^e. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

A variety of compounds in the present invention may exist in particular geometric or stereoisomeric forms. The present invention takes into account all such compounds, including cis- and trans isomers, R- and S- enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as being covered within the scope of this invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention. The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. When required, separation of the racemic material can be achieved by methods known in the art. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of

substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "electronically neutral" refers to a stable compound having no charge.

As used herein, "alkyl" or "alkylene" used alone or as a suffix or prefix, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having from 1 to 12 carbon atoms or if a specified number of carbon atoms is provided then that specific number would be intended. For example "C_{1-6} alkyl" denotes alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl. As used herein, "C_{1-3} alkyl", whether a terminal substituent or an alkylene group linking two substituents, is understood to specifically include both branched and straight-chain methyl, ethyl, and propyl.

As used herein "alkylhydroxy" represents an alkyl group straight chain or branched as defined above with the indicated number of carbon atoms with one or more hydroxy groups attached. One such example of alkylhdroxy would be $-CH_2OH$.

As used herein, the term "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. These may include fused or bridged polycyclic systems. Preferred cycloalkyls have from 3 to 10 carbon atoms in their ring structure, and more preferably have 3, 4, 5, and 6 carbons in the ring structure. For example, "C_{3-6} cycloalkyl" denotes such groups as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, "alkenyl" or "alkenylene" is intended to include from 2 to 12 hydrocarbon atoms of either a straight or branched configuration with one or more carbon-carbon double bonds that may occur at any stable point along the chain. Examples of "C_{3-6}alkenyl" include, but are not limited to, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 2-pentenyl, 3-pentenyl, hexenyl.

As used herein, "alkynyl" or "alkynylene" is intended to include from 2 to 12 hydrocarbon chains of either a straight or branched configuration with one or more carbon-carbon triple bonds that may occur at any stable point along the chain. Examples of alkynyl include but are not limited to ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl.

As used herein, the term "alkylcycloalkyl" is intended to mean an alkyl attached to the formula atom modified with a cycloalkyl. Examples of alkylcycloalkyl include, but are not limited to cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclopropylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, cyclopropylpropyl, cyclopentylpropyl, cyclohexylpropyl, cycloheptylpropyl.

As used herein, "cycloalkenyl" refers to ring-containing hydrocarbyl groups having at least one carbon-carbon double bond in the ring, and having from 3 to 12 carbons atoms.

As used herein, "cycloalkynyl" refers to ring-containing hydrocarbyl groups having at least one carbon-carbon triple bond in the ring, and having from 7 to 12 carbons atoms.

As used herein, the term "aralkyl" refers to an alkyl group substituted with an aryl group (an aromatic or heteroaromatic group).

As used herein, "aromatic" refers to hydrocarbyl groups having one or more polyunsaturated carbon rings having aromatic character, (e.g., 4n + 2 delocalized electrons) and comprising up to about 14 carbon atoms.

The term "aryl" as used herein includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, furan, imidazole, isoxazole, nicotinic, isonictinic, oxazole, phenyl, pyrazole, pyrazine, pyridazine, pyridine, pyrimidine, thiazole, thiophene, triazole and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "heteroaryl" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above. The term

"aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, for example, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms ortho, meta and para apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

As used herein, the term "heterocycle" or "heterocyclic" or "heterocyclyl" refers to a ring-containing monovalent and divalent structures having one or more heteroatoms, independently selected from N, O and S, as part of the ring structure and comprising from 3 to 20 atoms in the rings, more preferably 3- to 7- membered rings. Heterocyclic groups may be saturated or unsaturated, containing one or more double bonds, and heterocyclic groups may contain more than one ring as in the case of polycyclic systems. The heterocyclic rings described herein may be substituted on carbon or on a heteroatom atom if the resulting compound is stable. If specifically noted, nitrogen in the heterocycle may optionally be quaternized. It is understood that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another.

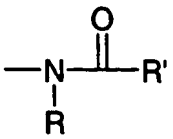
Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H, 6H-1, 5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1, 2,5-thiadiazinyl, acridinyl, azetidine, aziridine, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzotriazolyl, benzotetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dioxolane, furyl, 2,3-dihydrofuran, 2,5-dihydrofuran, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, homopiperidinyl, imidazolidine, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxirane, oxazolidinylperimidinyl, phenanthridinyl,

phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, purinyl, pyranyl, pyrrolidine, pyrroline, pyrrolidine, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, N-oxide-pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, pyridine, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, thiophane, thiotetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, thiirane, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl.

The terms "polycyclyl" or "polycyclic group" refer to two or more rings (for example, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and /or heterocyclyls) in which two or more carbons are common to two adjoining rings, for example, the rings are "fused rings." Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, carbonyl, carboxyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane, substituted piperazine.

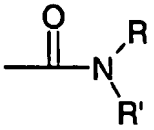
As used herein, the term "amine" or "amino" refers to groups of the general formula –NRR', wherein R and R' are each independently represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, aralkyl, or heteroaralkyl. Example of the amino group include, but are not limited to NH_2, methylamine, ethylamine, dimethylamine, diethylamine, propylamine, benzylamine and the like.

As used herein, the term "acylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R and R' are each independently represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heteroaralkyl.

As used herein, the term "amido" is art-recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:

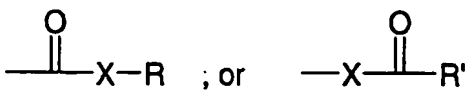


wherein R and R' are each independently represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heteroaralkyl, or R and R' may form a ring.

As used herein, "alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy, n-pentoxy, isopentoxy, cyclopropylmethoxy, allyloxy and propargyloxy. Similarly, "alkylthio" or "thioalkoxy" represent an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

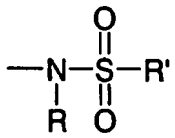
As used herein, the term "acyl" refers to groups of the of the general formula –C(=O)-R, wherein R is hydrogen, hydrocarbyl radical. Examples of acyl groups include, but are not limited to acetyl, propionyl, benzoyl, phenyl acetyl.

As used herein, the term "carbonyl" is art recognized and includes such moieties as can be represented by the general formula:



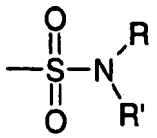
wherein X is a bond or represents an oxygen or sulfur, and R represents a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R''$ or a pharmaceutically acceptable salt, R' represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R''$, where m is an integer less than or equal to ten, and R'' is alkyl, cycloalkyl, alkenyl, aryl, or heteroaryl. Where X is an oxygen and R and R' is not hydrogen, the formula represents an "ester". Where X is an oxygen, and R is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R' is a hydrogen, the formula represents a "carboxylic acid." Where X is oxygen, and R' is a hydrogen, the formula represents a "formate." In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X is a sulfur and R and R' is not hydrogen, the formula represents a "thiolester." Where X is sulfur and R is hydrogen, the formula represents a "thiolcarboxylic acid." Where X is sulfur and R' is hydrogen, the formula represents a "thiolformate." On the other hand, where X is a bond, and R is not a hydrogen, the above formula represents a "ketone" group. Where X is a bond, and R is hydrogen, the above formula is represents an "aldehyde" group.

As used herein, the term "sulfonylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



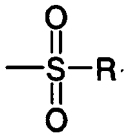
wherein R and R' are each independently represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heteroaralkyl.

As used herein, the term "sulfamoyl" is art-recognized and refers to a moiety that can be represented by the general formula:



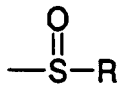
wherein R and R' are each independently represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heteroaralkyl, or R and R' may form a ring.

As used herein, the term "sulfonyl" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R is represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, aralkyl, or heteroaralkyl.

As used herein, the term "sulfoxido" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R is represented by but not limited to hydrogen, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, aralkyl, or heteroaralkyl.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo. "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, tosylate, benezensulfonate, and the like.

As used herein, "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example --C_vF_w where v=1 to 3 and w=1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, heptafluoropropyl, and heptachloropropyl. "Haloalkoxy" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge; for example

trifluoromethoxy, pentafluoroethoxy, 2,2,2-trifluoroethoxy, and the like. "Haloalkylthio" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, "moieties" means alkyl; cycloalkyl; alkenyl; alkynyl; alkylcycloalkyl; cycloalkenyl; cycloalkynyl; aralkyl; aryl; heterocycle; polycyclyl; amine;acylamino; amido; alkoxy; acyl; carbonyl; sulfonylamino; sulfamoyl; sulfonyl; sulfoxido; halo; haloalkyl; haloalkoxy as these terms are defined herein.

As used herein, the phrase "protecting group" means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999)..

As used herein, "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic,

phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, maleic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

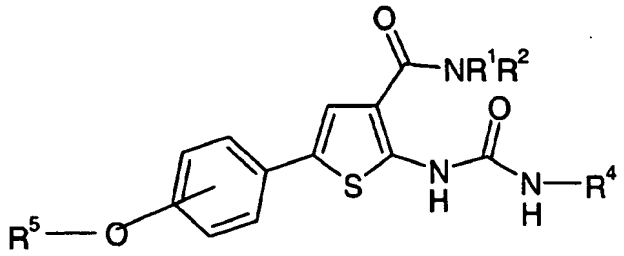
The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers that release the active parent drug according to formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

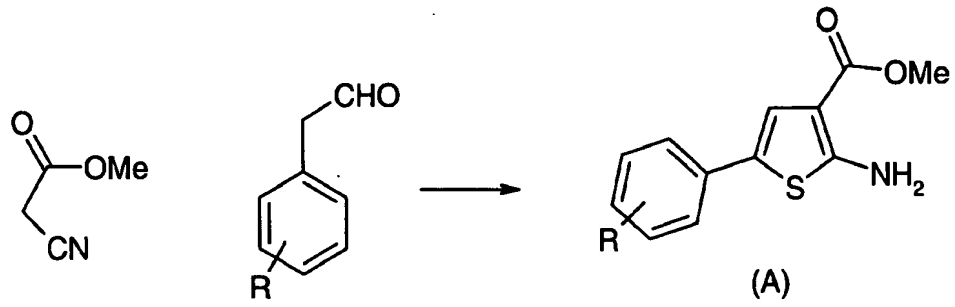
Detailed description of the invention

In a first embodiment, the present invention provides novel compounds having structural diagram (I):



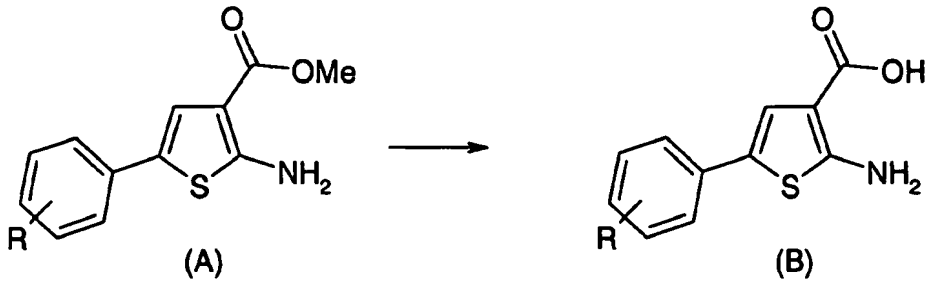
(I)

In an additional embodiment the present invention provides a process for preparing a compound of formula (I) as recited above or a pharmaceutically acceptable salt or an in vivo hydrolysable ester therof which process comprises:

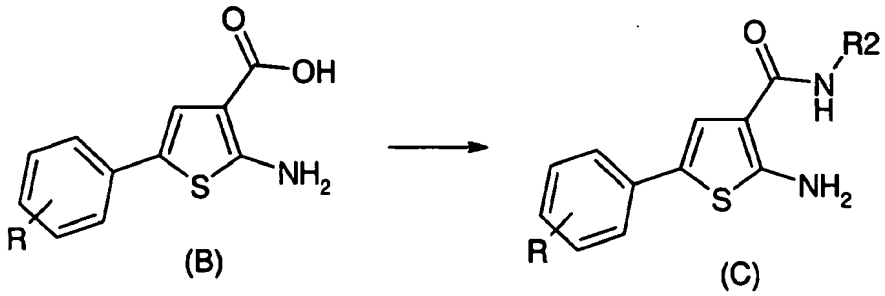


(A)

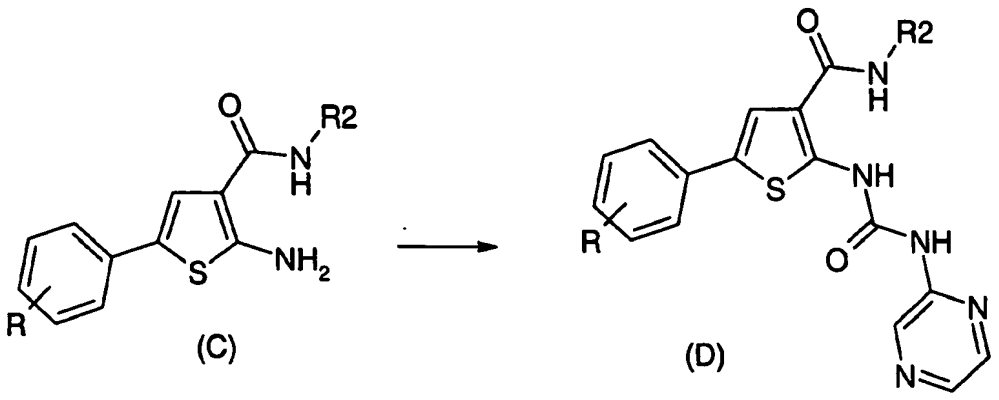
Triethylamine (1 equivalent) was added dropwise to a suspension of sulfur, methyl cyanoacetate and the requisite phenylacetaldehyde (1 equivalent each) in anhydrous DMF. The reaction was heated at 50oC for approximately 1.5hours. The solution was poured onto crushed ice with vigorous stirring to precipitate the product (A), which was filtered off, washed with water and dried at 50oC under high vacuum.



To a suspension of the thiophene (A) in dichloromethane was added a solution of BBr3 (5 equivalents). The reaction vessel was flushed with nitrogen and sealed. The mixture was sonicated for one hour, cooled and quenched by the addition of 1N HCl. The crude reaction mixture was concentrated under reduced pressure and the desired product (B) isolated by column chromatography.



A solution of the acid (B) in DMF was added dropwise into a DMF solution of hydroxybenzotriazole, diisopropylcarbodiimide and R_2NH_2 (3 equivalents of each). The reaction was stirred at room temperature overnight. After this time, reaction was complete (LC/MS), so the mixture was poured into water and extracted with ethyl acetate. The organic phase was separated, washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the desired amide (C) isolated by column chromatography.



To a DMF solution of the starting amine (C) was added pyrazinecarboxylic acid (3 equivalents) and triethylamine (10 equivalents). The mixture was heated at 90oC in an oil bath, and diphenylphosphorylazide added dropwise. The mixture was stirred at 90oC for an hour after which time reaction was complete (LC/MS). The mixture was cooled to room temperature, poured into water and extracted with ethyl acetate. The organic phase was separated, washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the desired urea (D) isolated by column chromatography.

Combinations

The anti-cancer treatment defined herein may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and

taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin) and cytodifferentiating agents(for example All-trans retinoic acid, 13-cis retinoic acid and fenretinide);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention.

Formulations

Compounds of the present invention may be administered orally, parenteral, buccal, vaginal, rectal, inhalation, insufflation, sublingually, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

An effective amount of a compound of the present invention for use in therapy of infection is an amount sufficient to symptomatically relieve in a warm-blooded animal, particularly a human the symptoms of infection, to slow the progression of infection, or to reduce in patients with symptoms of infection the risk of getting worse.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers include magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Some of the compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bicarbonate, bisulfate, butyrate, camphorate, camphorsulfonate, choline, citrate, cyclohexyl sulfamate, diethylenediamine, ethanesulfonate, fumarate, glutamate, glycolate, hemisulfate, 2-hydroxyethylsulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, meglumine, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate, phenylacetate, phosphate, diphosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-toluenesulfonate), trifluoroacetate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as aluminum, calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, ornithine, and so forth. Also, basic nitrogen-containing groups may be

quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl halides; dialkyl sulfates like dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl halides; aralkyl halides like benzyl bromide and others. Non-toxic physiologically-acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion-exchange resin.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

In addition to the compounds of the present invention, the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to herein.

The term composition is intended to include the formulation of the active component or a pharmaceutically acceptable salt with a pharmaceutically acceptable carrier. For example this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

Liquid form compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for

oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

The pharmaceutical compositions can be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Synthesis

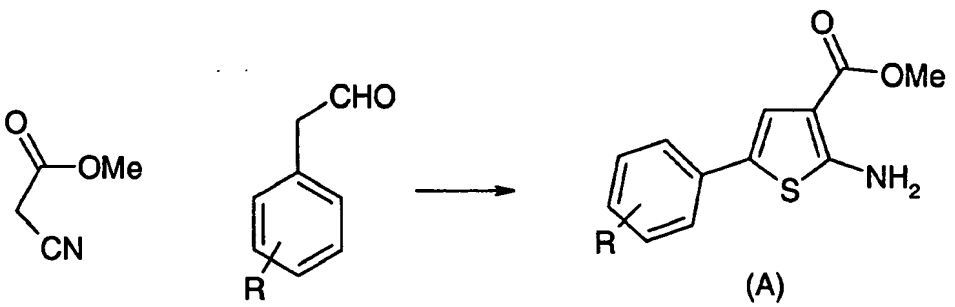
The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Such methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described herein. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents, which are not compatible with the reaction conditions, will be readily apparent to one skilled in the art and alternate methods must then be used.

The starting materials for the Examples contained herein are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials and examples used herein.

General procedures for making the compounds of the invention is as follows:

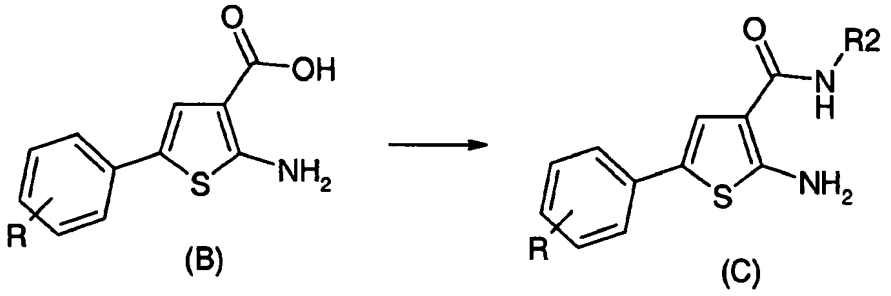
Scheme 1



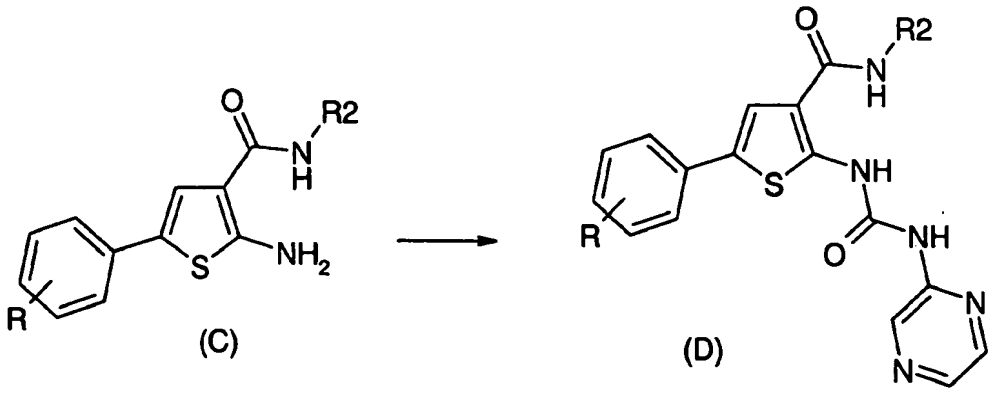
(A)

Triethylamine (1 equivalent) was added dropwise to a suspension of sulfur, methyl cyanoacetate and the requisite phenylacetaldehyde (1 equivalent each) in anhydrous DMF. The reaction was heated at 50oC for approximately 1.5hours. The solution was poured onto crushed ice with vigorous stirring to precipitate the product (A), which was filtered off, washed with water and dried at 50oC under high vacuum.

To a suspension of the thiophene (A) in dichloromethane was added a solution of BBr3 (5 equivalents). The reaction vessel was flushed with nitrogen and sealed. The mixture was sonicated for one hour, cooled and quenched by the addition of 1N HCl. The crude reaction mixture was concentrated under reduced pressure and the desired product (B) isolated by column chromatography.



A solution of the acid (B) in DMF was added dropwise into a DMF solution of hydroxybenzotriazole, diisopropylcarbodiimide and R_2NH_2 (3 equivalents of each). The reaction was stirred at room temperature overnight. After this time, reaction was complete (LC/MS), so the mixture was poured into water and extracted with ethyl acetate. The organic phase was separated, washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the desired amide (C) isolated by column chromatography.



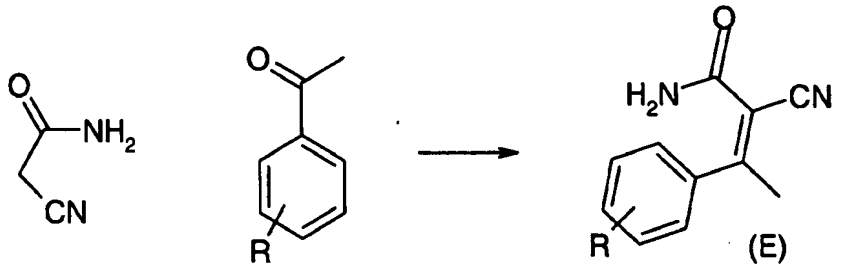
To a DMF solution of the starting amine (C) was added pyrazinecarboxylic acid (3 equivalents) and triethylamine (10 equivalents). The mixture was heated at 90oC in an oil bath, and

diphenylphosphorylazide added dropwise. The mixture was stirred at 90oC for an hour after which time reaction was complete (LC/MS). The mixture was cooled to room temperature, poured into water and extracted with ethyl acetate. The organic phase was separated, washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the desired urea (D) isolated by column chromatography.

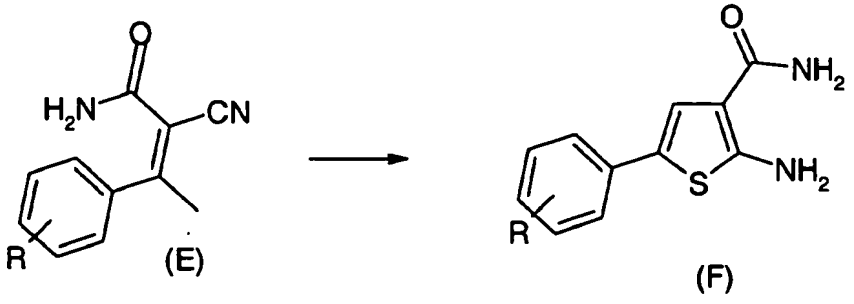
N-BOC deprotection

The N-BOC amides prepared above were deprotected under standard conditions (2N HCl).

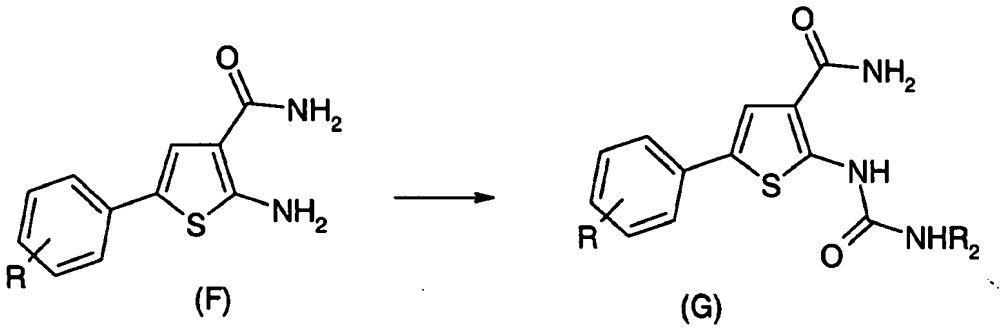
Scheme 2



The relevant substituted acetophenone (1 equivalent) and cyanoacetamide (1 equivalent) were dissolved in anhydrous toluene and ammonium acetate (0.2 equivalents) followed by glacial acetic acid (0.85 equivalents) added. The reaction was heated to reflux under Dean-Stark conditions to yield the intermediate (E) following standard work-up.



Intermediate (E) (1 equivalent) and sulfur (2 equivalents) were suspended in anhydrous ethanol. Diethylamine (1.2 equivalents) was added dropwise and the the mixture heated at 60oC for four days. The mixture was cooled, diluted with ethyl acetate and washed with water and brine. The organic phase was separated, dried over sodium sulfate and the solvent removed under reduced pressure. The desired product (F) was isolated by flash column chromatography.



To a DMF solution of the starting amine (F) was added the relevant carboxylic acid (3 equivalents) and triethylamine (10 equivalents). The mixture was heated at 90oC in an oil bath, and diphenylphosphorylazide added dropwise. The mixture was stirred at 90oC for an hour after which time reaction was complete (LC/MS). The mixture was cooled to room temperature, poured into water and extracted with ethyl acetate. The organic phase was separated, washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the desired urea (G) isolated by column chromatography.

Examples:

Examples 1-12

Name	Synthesis	R-NHBOC

5-(4-methoxyphenyl)-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	scheme 1	tert-butyl piperidin-4-ylcarbamate
5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	scheme 1	tert-butyl piperidin-4-ylcarbamate
5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide	scheme 1	tert-butyl (3S)-pyrrolidin-3-ylcarbamate
tert-butyl 3-{[(5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}thien-3-yl)carbonyl]amino}piperidine-1-carboxylate	scheme 1	tert-butyl 3-aminopiperidine-1-carboxylate
5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	scheme 1	tert-butyl 3-aminopiperidine-1-carboxylate
5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	scheme 1	tert-butyl 3-aminopiperidine-1-carboxylate
5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide	scheme 1	(S)-tert-butyl pyrrolidin-3-ylcarbamate

5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide	scheme 1	(S)-tert-butyl pyrrolidin-3-ylcarbamate
N-azepan-3-yl-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	scheme 1	tert-butyl azepan-3-ylcarbamate
N-[3-[(3-aminopyrrolidin-1-yl)carbonyl]-5-(4-methoxyphenyl)thien-2-yl]-N'-pyrazin-2-ylurea	scheme 1	tert-butyl 3-aminopyrrolidine-1-carboxylate
N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)thien-2-yl]-N'-pyrazin-2-ylurea	scheme 1	tert-butyl 1,4-diazepane-1-carboxylate
N-(2-aminoethyl)-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	scheme 1	tert-butyl (2-aminoethyl)carbamate

Examples 13-18

Name	Synthesis	RCO2H
2-({[(4-methoxyphenyl)amino]carbonyl}amino)-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]thiophene-3-carboxamide	scheme 2	4-methoxy benzoic acid
5-{4-[2-(dimethylamino)ethoxy]phenyl}-2-({[(4-methoxyphenyl)amino]carbonyl}amino)thiophene-3-carboxamide	scheme 2	4-methoxy benzoic acid
5-{4-[2-(diethylamino)ethoxy]phenyl}-2-({[(4-methoxyphenyl)amino]carbonyl}amino)thiophene-3-carboxamide	scheme 2	4-methoxy benzoic acid
2-({[(4-methoxyphenyl)amino]carbonyl}amino)-5-[4-(2-piperidin-1-ylethoxy)phenyl]thiophene-3-carboxamide	scheme 2	4-methoxy benzoic acid
5-{4-[2-(dimethylamino)ethoxy]phenyl}-2-{[(pyridin-3-ylamino)carbonyl]amino}thiophene-3-carboxamide	scheme 2	3-pyridine carboxylic acid
5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide	scheme 2	pyrazine carboxylic acid

Example 13

5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid (S)-piperidin-3-ylamide

(S)-3-{[5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester. To a solution of 5-(4-Methoxy-phenyl)-2-[3-(2,2,2-trichloro-acetyl)-ureido]-thiophene-3-carboxylic acid methyl ester (1.0 g, 2.2 mmol) in dry THF (20 mL) was added a solution of [Me_2Al-3-Boc-(S)-3-aminopiperidine] in THF (which was preformed by the addition of Me_3Al (2.0M in hexanes, 2.2 mL, 4.4 mmol) to a solution of (S)-3-Amino-piperidine-1-carboxylic acid tert-butyl ester (0.89 g, 4.4 mmol) in 10 mL THF at -78°C followed by warming to room temperature for an additional 15 min). The resulting orange-colored solution was stirred overnight at room temperature. The reaction mixture was cooled with ice and a 10% aqueous solution of Rochelle's salt was added slowly to quench the reaction. The resulting biphasic solution was warmed to room temperature and stirred for an additional 1h. The mixture was diluted with EtOAc and H_2O, the aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with H_2O, brine and dried (Na_2SO_4). Evaporation gave a pale orange solid. Purification by column chromatography (SiO_2, 50 % EtOAc/hexanes) gave 0.70 g (67%) of a light yellow solid. LC/MS (APCI, ES, M+H=475).

5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid (S)-piperidin-3-ylamide; hydrochloride. To a stirred solution of (S)-3-{[5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (0.70 g, 1.47 mmol) in anhydrous MeOH (5.0 mL) was added 4.0N HCl in 1, 4-dioxane (10 mL). A small amount of precipitate forms shortly and the reaction is stirred for an additional 4h at room temperature. The solvent was removed under vacuum. The residue was redissolved in methanol and concentrated under vacuum (2x) to yield 0.51 g (85%) of a light yellow solid. ^{1}H NMR (d_6-DMSO δ 10.9, s, 1H; δ 9.39, br s, 1H; δ 9.20, br s, 1H; δ 8.37, d, 1H; δ 7.88, s, 1H; δ 7.49, d, 2H; δ 6.96, d, 2H; δ 6.97, br s, 2H; δ 4.24, m, 1H; δ 3.77, s, 3H; δ 3.29, m, 1H; δ 3.11, m, 1H; δ 2.93, m, 2H; δ 1.91, m, 2H; δ 1.68, m, 2H), LC/MS (APCI, ES, M+H=3675).

Example 14

5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid (S)-azepan-3-ylamide

(S)-3-{[5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carbonyl]-amino}-azepane-1-carboxylic acid tert-butyl ester. To a solution of 5-(4-Methoxy-phenyl)-2-[3-(2,2,2-trichloro-acetyl)-ureido]-thiophene-3-carboxylic acid methyl ester (1.36 g, 3 mmol) in anhydrous THF (20 mL) was added a solution of [Me_2Al-3-Boc-(S)-3-aminohomopiperidine] in THF (preformed by the careful addition of Me_3Al (2.0M in hexanes, 3.0 mL, 6.0 mmol) to a solution of (S)-3-Amino-azepane-1-carboxylic acid tert-butyl ester in 10 mL of THF at -78°C followed by warming to room temperature under nitrogen and stirring for an additional 15 min.). The resulting deep yellow/orange solution was stirred overnight at room temperature. The reaction mixture was cooled with ice and a 10% aqueous solution of Rochelle's salt was added slowly to quench the reaction. The resulting biphasic solution was warmed to room temperature and stirred for an additional 1h. The mixture was diluted with EtOAc and H_2O, the aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with H_2O, brine and dried (Na_2SO_4). Evaporation gave a pale orange solid. Purification by ISCO MPLC (SiO_2, 60-80% EtOAc/hexanes) gave 0.9 g (62%) of the title compound as a white solid. ^{1}H NMR (d_6-DMSO, δ 11.0, s, 1H; δ 7.95, d, 0.5H; δ 7.81, d, 0.5H; δ 7.65, s, 0.5H; δ 7.56, s, 0.5H; δ 7.46, d, 2H; δ 6.97, d, 2H; δ 6.96, br s, 2H; δ 4.19, m, 0.5H; δ 4.11, m, 0.5H; δ 3.77, m, 3H; δ 3.65, m, 1H; δ 3.48, m, 1H; δ 3.20, m, 2H; δ 1.75, m, 3H; δ 1.58, m, 2H; δ 1.42, s, 4.5H; δ 1.39, m, 1H; δ 1.36, s, 4.5H), LC/MS (APCI, ES, M+H=489).

5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid (S)-azepan-3-ylamide; hydrochloride. To a stirred solution of (S)-3-{[5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carbonyl]-amino}-azepane-1-carboxylic acid tert-butyl ester (0.9g, 1.8 mmol) in 1, 4-dioxane (10 mL) was added 4.0N HCl in 1, 4-dioxane (10 mL, 40 mmol). A precipitate forms shortly and the reaction is stirred for an additional 4h at room temperature. Due to the hygroscopic nature of the salt form, the solvent was removed under vacuum. The residue was dissolved in methanol and concentrated under vacuum (2x) to yield and off-white solid. Recrystallization from using 2-propanol gave 0.45g (59%) of a white solid. ^{1}H NMR (d_6-DMSO, δ 10.9, s, 1H; δ 9.58, br s, 1H; δ 9.29, br s, 1H; δ 8.39, d, 1H; δ 7.82, s, 1H; δ 7.48, d, 2H; δ 6.96, d, 2H; δ 4.36, m, 1H; δ 3.77, s, 3H; δ 3.29, m, 1H; δ 3.20, m, 2H; δ 3.07, m, 1H; δ 1.98, m, 1H; δ 1.84, m, 4H; δ 1.59, m, 1H), LC/MS (APCI, ES, M+H=389).

Example 15

5-(4-Methoxy-phenyl)-2-(3-pyrazin-2-yl-ureido)-thiophene-3-carboxylic acid (S)-azepan-3-ylamide

S)-3-{[5-(4-Methoxy-phenyl)-2-(3-pyrazin-2-yl-ureido)-thiophene-3-carbonyl]-amino}-azepane-1-carboxylic acid tert-butyl ester. A solution of (S)-3-{[2-Amino-5-(4-methoxy-phenyl)-thiophene-3-carbonyl]-amino}-azepane-1carboxylic acid tert-butyl ester (0.76 g, 1.7 mmol) and pyrazine-2-carbonyl azide (0.5 g, 3.4 mmol) in 20 mL of anhydrous DME was refluxed for 2h. The solvent was removed under reduced pressure and the crude product was purified using ISCO MPLC (40-60% EtOAc/hexanes) to give the title 0.51 g (53%) compound as a light yellow solid. ^{1}H NMR (d_6-DMSO δ 12.5, br s, 0.5H; δ 12.4, br s, 0.5H; δ 10.90, s, 0.5H; δ 10.88, s, 0.5H; δ 8.93, s, 0.5H; δ 8.89, s, 0.5H; δ 8.33, d, 1H; δ 8.29, t, 1H; δ 8.05, d, 0.5H; δ 7.91, d, 0.5H; δ 7.74, s, 0.5H; δ 7.65, s, 0.5H; δ 7.52, dd, 2H; δ 7.00, d, 2H; δ 4.26, m, 0.5H; δ 4.17, m, 0.5H; δ 3.79, s, 3H; δ 3.69, m, 1H; δ 3.48, m, 1H; δ 3.21, m, 2H; δ 1.77, m, 3H; δ 1.61, m, 2H; δ 1.44, s, 4.5H; δ 1.38, s+m, 5.5H), LC/MS (APCI, ES, M+H=567).

5-(4-Methoxy-phenyl)-2-(3-pyrazin-2-yl-ureido)-thiophene-3-carboxylic acid (S)-azepan-3-ylamide; hydrochloride. To a stirred solution of (S)-3-{[5-(4-Methoxy-phenyl)-2-(3-pyrazin-2-yl-ureido)-thiophene-3-carbonyl]-amino}-azepane-1-carboxylic acid tert-butyl ester (0.51 g, 0.9 mmol) in 10 mL of MeOH is added 10 mL (40 mmol) of 4.0 N HCl in dioxane. The solution was stirred at room temperature for 4h and then concentrated under vacuum. The residue was partially recrystallized by triturating in refluxing 2-propanol to yield the title compound are a light orange solid (0.30 g, 67%). ^{1}H NMR (d_6-DMSO δ 12.6, br s, 1H; δ 10.9, s, 1H; δ 9.55, br s, 1H; δ 9.24, br s, 1H; δ 8.88, s, 1H; δ 8.49, d, 1H; δ 8.35, dd, 1H; δ 8.29, d, 1H; δ 7.92, s, 1H; δ 7.54, d, 2H; δ 6.99, d, 2H; δ 4.42, m, 1H; δ 3.33, m, 1H; δ 3.23, m, 2H; δ 3.10, m, 1H; δ 2.02, m, 1H; δ 1.85, m, 4H; δ 1.62, m, 1H;), LC/MS (APCI, ES, M+H=467).

Examples 16-45

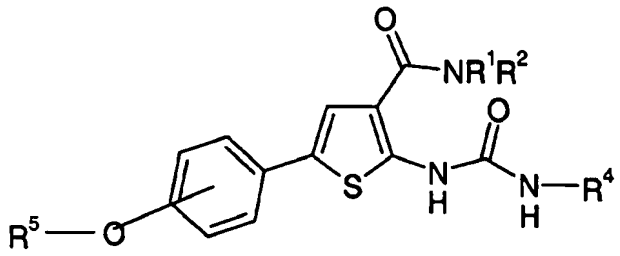
Examples 16-45 were prepared in a similar fashion to that described for example 15.

Utility

The compounds of the present invention have utility for the treatment of neoplastic disease by acting upon checkpoint kinase. Methods of treatment target checkpoint kinase activity. Thus, inhibitors of checkpoint kinase have been shown to allow cells to progress inappropriately to the metaphase of mitosis leading to apoptosis of effected cells, and to therefore have anti-proliferative effects. Thus checkpoint kinase inhibitors act as modulators of cell division and are expected to be active against neoplastic disease such as carcinoma of the brain, breast, ovary, lung, colon, prostate, skin or other tissues, as well as leukemias and lymphomas, tumors of the central and peripheral nervous system, and other tumor types such as melanoma, sarcomas, fibrosarcoma and osteosarcoma. Checkpoint kinase inhibitors are also expected to be useful for the treatment other proliferative diseases including but not limited to autoimmune, inflammatory, neurological, and cardiovascular diseases.

Claims

1. A compound of structural formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 are at each occurrence independently selected from H, optionally substituted C_{1-6}alkyl, or optionally substituted heterocycle; or R^1 and R^2 and the N to which they are attached in combination form an optionally substituted heterocycle with the proviso that R^1 and R^2 are not both H;

R^4 is selected from H, optionally substituted carbocycle, optionally substituted heterocycle, or optionally substituted C_{1-6}alkyl;

R^5 is selected from optionally substituted carbocycle, or optionally substituted C_{1-6}alkyl.

2. A compound of formula (I) selected from:

2-({[(4-methoxyphenyl)amino]carbonyl}amino)-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]thiophene-3-carboxamide;

5-{4-[2-(dimethylamino)ethoxy]phenyl}-2-({[(4-methoxyphenyl)amino]carbonyl}amino)thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-2-({[(4-methoxyphenyl)amino]carbonyl}amino)thiophene-3-carboxamide;

2-({[(4-methoxyphenyl)amino]carbonyl}amino)-5-[4-(2-piperidin-1-ylethoxy)phenyl]thiophene-3-carboxamide;

5-{4-[2-(dimethylamino)ethoxy]phenyl}-2-{[(pyridin-3-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-(4-methoxyphenyl)-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

tert-butyl 3-{[(5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}thien-3-yl)carbonyl]amino}piperidine-1-carboxylate;

5-{3-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-3-yl-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

5-{4-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

5-{3-[2-(diethylamino)ethoxy]phenyl}-2-{[(pyrazin-2-ylamino)carbonyl]amino}-N-[(3S)-pyrrolidin-3-yl]thiophene-3-carboxamide;

N-azepan-3-yl-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

N-[3-[(3-aminopyrrolidin-1-yl)carbonyl]-5-(4-methoxyphenyl)thien-2-yl]-N'-pyrazin-2-ylurea;

N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)thien-2-yl]-N'-pyrazin-2-ylurea;

N-(2-aminoethyl)-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;

Tert-butyl-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)thien-3-yl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-piperidin-3-ylthiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-(1-methylpiperidin-4-yl)thiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-[4-methoxyphenyl)thiophene-3-carboxaminde;

2-[(aminocarbonyl)amino]-5-(3,4-dihydroxyphenyl)-N-piperidin-4-ylthiophene-3-carboxaminde;
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxaminde;
Tert-butyl-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}thien-3-yl)carbonyl]amino)piperidine-1-carboxylate;
Tert-butyl-3-{[(2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl}thien-3-yl)carbonyl]amino)piperidine-1-carboxylate;
2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]thiophene-3-carboxaminde;
2-[(aminocarbonyl)amino]-5-(4-[2-(diethylamino)ethoxy]phenyl}-N-piperidin-4-ylthiophene-3-carboxaminde;
2-[(aminocarbonyl)amino]-5-{3-[2-(diethylamino)ethoxy]phenyl} N-piperidin-3-ylthiophene-3-carboxaminde;
2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-phenylthiophene-3- carboxaminde;
2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-(3,4-dimethoxyphenyl)thiophene-3- carboxaminde;
2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-bromothiophene-3- carboxaminde;
Tert-butyl-3(S)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}thien-3-yl)carbonyl]amino}piperdine-1-carboxylate
2-[(aminocarbonyl)amino]-5-(4-[2-(diethylamino)ethoxy]phenyl)-N-[(3S)-piperidin-3-yl]thiophene-3-carboxaminde;
2-[(aminocarbonyl)amino]-5-(4-[2-(diethylamino)ethoxy]phenyl)-N-[(3R)-piperidin-3-yl]thiophene-3-carboxaminde;
N-2-[(aminoethyl)-5-(4-methoxyphenyl)-2-{[(pyrazin-2-ylamino)carbonyl]amino}thiophene-3-carboxamide;
2-[(aminocarbonyl)amino]-N-azepan-3-yl-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxaminde;
5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid (S)-piperidin-3-ylamide;
5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid (S)-azepan-3-ylamide;
5-(4-Methoxy-phenyl)-2-(3-pyrazin-2-yl-ureido)-thiophene-3-carboxylic acid (S)-azepan-3-ylamide;

tert-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-[(2*S*)-pyrrolidin-2-ylmethyl]thiophene-3-carboxamide;;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-pyrrolidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-(2-piperidin-1-ylethyl)thiophene-3-carboxamide;

tert-butyl (3*S*)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)pyrrolidine-1-carboxylate;

tert-butyl (3*R*)-3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-(1,2,3,4-tetrahydroquinolin-3-yl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*S*)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide*tert*-butyl 3-({[2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-3-thienyl]carbonyl}amino)azetidine-1-carboxylate;

2-[(aminocarbonyl)amino]-*N*-azetidin-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-*N*-pyrrolidin-3-ylthiophene-3-carboxamide;

tert-butyl 3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-[(3*R*)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-*N*-piperidin-3-ylthiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*S*)-azepan-3-yl]-5-(3,4-dimethoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-1-azabicyclo[2.2.2]oct-3-yl-5-(4-methoxyphenyl)thiophene-3-carboxamide;

N-[3-(1,4-diazepan-1-ylcarbonyl)-5-(4-methoxyphenyl)-2-thienyl]urea;

2-[(aminocarbonyl)amino]-*N*-(1-ethylpiperidin-3-yl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

tert-butyl (3*S*)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

tert-butyl (3*R*)-3-{[(2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-3-thienyl)carbonyl]amino}piperidine-1-carboxylate;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-*N*-[(3*S*)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-{4-[2-(diethylamino)ethoxy]phenyl}-*N*-[(3*R*)-piperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*S*)-azepan-3-yl]-5-{4-[2-(diethylamino)ethoxy]phenyl}thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*S*)-1-ethylazepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-(2-aminoethyl)-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[2-(dimethylamino)ethyl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-[(3*R*)-azepan-3-yl]-5-(4-methoxyphenyl)thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-[(3*S*)-1-methylpiperidin-3-yl]thiophene-3-carboxamide;

2-[(aminocarbonyl)amino]-5-(4-methoxyphenyl)-*N*-[(3*S*)-1-methylazepan-3-yl]thiophene-3-carboxamide;

N-[3-{[(3*S*)-3-aminoazepan-1-yl]carbonyl}-5-(4-methoxyphenyl)-2-thienyl]urea.

3. A compound according to any one of claims 1 to 2, for use as a medicament.

4. The use of a compound as defined in any one of claims 1 to 2, in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with cancer.

5. A method for the treatment of infections associated with cancer comprising administering to a host in need of such treatment a therapeutically effective amount of a compound as defined in any one of claims 1 to 2.

6. A method for the prophylaxis treatment of infections associated with cancer comprising administering to a host in need of such treatment a therapeutically effective amount of a compound as defined in any one of claims 1 to 2.

7. A method for the treatment or prophylaxis of cancer comprising administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 2 or a pharmaceutically acceptable salt.

8. A method for the treatment of breast cancer, colorectal cancer, ovarian cancer, lung (non small cell) cancer, malignant brain tumors, sarcomas, melanoma and lymphoma by administring a compound of formula I as recited in claim 1.

9. A method for the treatment of breast cancer, colorectal cancer, ovarian cancer, lung (non small cell) cancer, malignant brain tumors, sarcomas, melanoma and lymphoma by administring a compound of formula I as recited in claim 2.

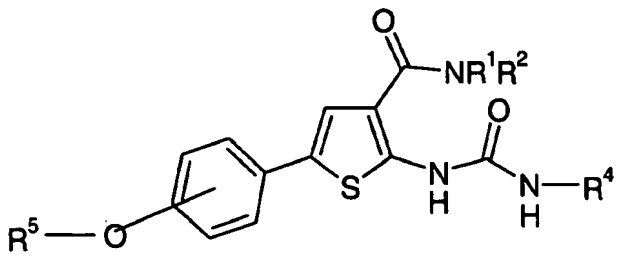
10. A method of treating cancer by administering to a human a compound of claim 1 to 2 and a DNA damaging agent.

11. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 2 together with at least one pharmaceutically acceptable carrier, diluent or excipent.

ABSTRACT

SUBSTITUTED THIOPHENES AND USES THEREOF

This invention relates to novel compounds having the structural formula (I)



(I)

and to their pharmaceutical compositions and to their methods of use. These novel compounds provide a treatment or prophylaxis of cancer.

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